L2 ANSWER 1 OF 12 MEDLINE
AN 1999343700 MEDLINE
DN 99343700 PubMed ID: 10413774
TI Traumatic brain injury in young, amyloid-beta peptide overexpressing **transgenic** mice induces marked ipsilateral hippocampal atrophy and diminished Abeta deposition during aging.
AU Nakagawa Y; Nakamura M; McIntosh T K; Rodriguez A; Berlin J A; Smith D H; Saatman K E; Raghupathi R; Clemens J; Saido T C; Schmidt M L; Lee V M; Trojanowski J Q
CS The Center for Neurodegenerative Disease Research, Division of Anatomic Pathology, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-4283, USA.
NC AG09215 (NIA)
AG11542 (NIA)
GM34690 (NIGMS)
+
SO JOURNAL OF COMPARATIVE NEUROLOGY, **(1999 Aug 30)** 411 (3) 390-8.
Journal code: HUV; 0406041. ISSN: 0021-9967.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012
AB Traumatic brain injury (TBI) is an epigenetic risk factor for Alzheimer's disease (AD). To test the hypothesis that TBI contributes to the onset and/or progression of AD-like **beta-amyloid** peptide (Abeta) deposits, we studied the long-term effects of TBI in **transgenic** mice that overexpress human Abeta from a mutant Abeta precursor protein (APP) minigene driven by a platelet derived (PD) growth factor promoter (PDAPP mice). TBI was induced in 4-month-old PDAPP and wild type (WT) mice by controlled cortical impact (CCI). Because Abeta begins to deposit progressively in the PDAPP brain by 6 months, we examined WT and PDAPP mice at 2, 5, and 8 months after TBI or sham treatment (i.e., at 6, 9, and 12 months of age). Hippocampal atrophy in the PDAPP mice was more severe ipsilateral versus contralateral to TBI, and immunohistochemical studies with **antibodies** to different Abeta peptides demonstrated a statistically significant reduction in hippocampus and cingulate cortex Abeta deposits ipsilateral versus contralateral to CCI in 9-12 month-old PDAPP mice. Hippocampal atrophy and reduced Abeta deposits were not seen in hippocampus or cingulate cortex of sham-injured PDAPP mice or in any WT mice. These data suggest that the vulnerability of brain cells to Abeta toxicity increases and that the accumulation of Abeta deposits decrease in the penumbra of CCI months after TBI. Thus, in addition to providing unique opportunities for elucidating genetic mechanisms of AD, **transgenic** mice that recapitulate AD pathology also may be relevant animal models for investigating the poorly understood role that TBI and other epigenetic risk factors play in the onset and/or progression of AD.


L2 ANSWER 2 OF 12 MEDLINE
AN 1999061414 MEDLINE
DN 99061414 PubMed ID: 9846957
TI **Transgenic** mice over-expressing the C-99 fragment of betaPP with

an alpha-secretase site mutation develop a myopathy similar to human inclusion body myositis.
CM Comment in: Am J Pathol. 1998 Dec;153(6):1673-7
AU Jin L W; Hearn M G; Ogburn C E; Dang N; Nochlin D; Ladiges W C; Martin G M
CS Department of Pathology, University of Washington, Seattle 98195-6480, USA.. lwjin@u.washington.edu
NC P50AG05136 (NIA)
R35AG10917 (NIA)
T32AG00057 (NIA)
+
SO AMERICAN JOURNAL OF PATHOLOGY, **(1998 Dec)** 153 (6) 1679-86.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981229
AB Inclusion body myositis (IBM) is the most common muscle disease in the elderly. Amyloid-beta protein (A beta) has been shown to accumulate abnormally in the vacuolated fibers and to localize to amyloid-like fibrils in muscles from IBM patients. We studied the skeletal muscles from a line of **transgenic** mice over-expressing the carboxyl-terminal 99 amino acids (C99) of the **beta-amyloid** precursor protein (betaPP) with a substitution of lysine-612 to valine (K612V), intended to abolish alpha-secretase recognition and to preserve the A beta domain of C99. The majority (87%) of the 24-month-old **transgenic** mice showed myopathic changes, and approximately one-third of them had degenerating fibers with sarcoplasmic vacuoles and thioflavin-S-positive deposits. Ultrastructurally, the inclusions were aggregates of short thin amyloid-like fibrils, 6 to 8 nm in diameter. These features are similar to those of human IBM. Immunocytochemistry using an **antibody** against A beta showed membranous staining in most muscle fibers of **transgenic** mice, as well as granular or vacuolar cytoplasmic staining in the atrophic fibers. Western blots showed a high level of accumulation of carboxyl-terminal fragments of betaPP in the muscles of the **transgenic** mice with the most severe IBM-like lesions. The expression of IBM-like lesions was age dependent. These **transgenic** mice provide a model for the study of IBM and for the peripheral expression of a key element in the pathogenesis of Alzheimer disease.

L2 ANSWER 3 OF 12 MEDLINE
AN 1998206422 MEDLINE
DN 98206422 PubMed ID: 9546346
TI Evidence of oxidative stress and in vivo neurotoxicity of **beta-amyloid** in a **transgenic** mouse model of Alzheimer's disease: a chronic oxidative paradigm for testing antioxidant therapies in vivo.
AU Pappolla M A; Chyan Y J; Omar R A; Hsiao K; Perry G; Smith M A; Bozner P
CS University of South Alabama, Mobile 36617, USA.. mpappoll@usamail.usouthal.edu
NC AG11130 (NIA)
SO AMERICAN JOURNAL OF PATHOLOGY, **(1998 Apr)** 152 (4) 871-7.

Journal code: 3RS; 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199804
ED Entered STN: 19980507
Last Updated on STN: 19980507
Entered Medline: 19980428
AB Increased expression of antioxidant enzymes and heat-shock proteins are key markers of oxidative stress. Such proteins are abnormally present within the neuropathological lesions of Alzheimer's disease (AD), suggesting that oxidative stress may play significant but yet undefined roles in this disorder. To gain further insight into the role of oxidative stress in AD, we studied the expression of CuZn superoxide dismutase (SOD) and hemoxygenase-1 (HO-1), two established markers of oxidative stress, in a **transgenic** mouse model of AD. Immunohistochemistry with anti-SOD and anti-HO-1 **antibodies** revealed a very pronounced increase of these proteins only in aged transgene-positive mice. Interestingly, the distribution of the oxidative burden was largely overlapping with dystrophic neuritic elements in the mice as highlighted with anti-ubiquitin **antibodies**. Because the most conspicuous alterations were identified around amyloid (Abeta) deposits, our results provide strong support for the hypothesis that Abeta is neurotoxic in vivo and that such toxicity is mediated by free radicals. To obtain additional experimental evidence for such an interpretation (ie, a cause-effect relationship between Abeta and oxidative neurotoxicity), PC12 cells were exposed to increasing concentrations of Abeta or to oxidative stress. In agreement with the in vivo findings, either treatment caused marked induction of SOD or HO-1 in a dose-dependent fashion. These results validate the **transgenic** approach for the study of oxidative stress in AD and for the evaluation of antioxidant therapies in vivo.

L2 ANSWER 4 OF 12 MEDLINE
AN 1998176743 MEDLINE
DN 98176743 PubMed ID: 9517566
TI Enhanced GFAP expression in astrocytes of **transgenic** mice expressing the human brain-specific trypsinogen IV.
AU Minn A; Schubert M; Neiss W F; Muller-Hill B
CS Institut fur Genetik, Lindenthal, Koln, Germany.
SO GLIA, **(1998 Apr)** 22 (4) 338-47.
Journal code: GLI; 8806785. ISSN: 0894-1491.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
ED Entered STN: 19980514
Last Updated on STN: 19980514
Entered Medline: 19980505
AB We recently identified a cDNA encoding a human brain specific trypsinogen (trypsinogen IV). In order to test whether trypsinogen IV is involved in CNS diseases of, or injury response in, mammalian brain, a mouse model was developed in which the human trypsinogen IV was expressed specifically in neurons. Immunocytochemical analysis of the brains of **transgenic**

mice revealed a striking enhancement of glial fibrillar acidic protein (GFAP) expression in astrocytes. This remarkable astrocytic reaction was detected in the brains of mice as young as 2 months and did not diminish in the older animals we tested. However, we did not find gross evidence for neurodegeneration, nor for reactive microglial cells. The long-term survival of these animals should provide a model with which to study the mechanism of nerve-astroglia interactions. In addition, the possible participation of trypsin IV in the metabolism of the Alzheimer precursor protein (APP) was investigated by immunostaining brains from **transgenic** mice with **beta-amyloid** (betaA4) **antibodies**. Immunocytochemical staining of brains from one year old **transgenic** mice revealed an intense intracellular betaA4-like signal in neurons.

L2 ANSWER 5 OF 12 MEDLINE
AN 1998037005 MEDLINE
DN 98037005 PubMed ID: 9370051
TI Animal models of cerebral **beta-amyloid** angiopathy.
AU Walker L C
CS Parke-Davis Pharmaceutical Research, Division of Warner-Lambert, Ann Arbor, MI 48105, USA.. walkerl@aa.wl.com
NC AG05146 (NIA)
NS20471 (NINDS)
SO BRAIN RESEARCH. BRAIN RESEARCH REVIEWS, **(1997 Sep 30)** 25 (1) 70-84. Ref: 166
Journal code: BRS; 8908638. ISSN: 0165-0173.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980109
AB Cerebral amyloid angiopathy (CAA) is a significant risk factor for hemorrhagic stroke in the elderly, and occurs as a sporadic disorder, as a frequent component of Alzheimer's disease, and in several rare, hereditary conditions. The most common type of amyloid found in the vasculature of the brain is **beta-amyloid** (A beta), the same peptide that occurs in senile plaques. A paucity of animal models has hindered the experimental analysis of CAA. Several **transgenic** mouse models of cerebral beta-amyloidosis have now been reported, but only one appears to develop significant cerebrovascular amyloid. However, well-characterized models of naturally occurring CAA, particularly aged dogs and non-human primates, have contributed unique insights into the biology of vascular amyloid in recent years. Some non-human primate species have a predilection for developing CAA; the squirrel monkey (Saimiri sciureus), for example, is particularly likely to manifest **beta-amyloid** deposition in the cerebral blood vessels with age, whereas the rhesus monkey (Macaca mulatta) develops more abundant parenchymal amyloid. These animals have been used to test in vivo **beta-amyloid** labeling strategies with monoclonal **antibodies** and radiolabeled A beta. Species-differences in the predominant site of A beta deposition also can be exploited to evaluate factors that direct amyloid selectively to a particular tissue compartment of the brain. For

example, the cysteine protease inhibitor, cystatin C, in squirrel monkeys has an amino acid substitution that is similar to the mutant substitution found in some humans with a hereditary form of cystatin C amyloid angiopathy, possibly explaining the predisposition of squirrel monkeys to CAA. The existing animal models have shown considerable utility in deciphering the pathobiology of CAA, and in testing strategies that could be used to diagnose and treat this disorder in humans.

L2 ANSWER 6 OF 12 MEDLINE
AN 97368345 MEDLINE
DN 97368345 PubMed ID: 9223340
TI Interaction between amyloid precursor protein and presenilins in mammalian cells: implications for the pathogenesis of Alzheimer disease.
AU Xia W; Zhang J; Perez R; Koo E H; Selkoe D J
CS Department of Neurology, Harvard Medical School, Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA 02115, USA.
NC AG05134 (NIA)
AG12376 (NIA)
AG12749 (NIA)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Jul 22)** 94 (15) 8208-13.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970908
Last Updated on STN: 19980206
Entered Medline: 19970827
AB Mutations in the presenilin 1 (PS1) and presenilin 2 (PS2) genes increase the production of the highly amyloidogenic 42-residue form of amyloid beta-protein (Abeta42) in a variety of cell lines and **transgenic** mice. To elucidate the molecular mechanism of this effect, wild-type (wt) or mutant PS1 and PS2 genes were stably transfected into Chinese hamster ovary cells expressing endogenous or transfected **beta-amyloid** precursor protein (APP). By immunoprecipitation/Western blot analysis, APP was consistently found to coimmunoprecipitate with PS1 or PS2 proteins. Several distinct PS1, PS2, or APP **antibodies** precipitated PS-APP complexes that were detectable by blotting with either APP or PS **antibodies**. Importantly, complex formation could be detected at endogenous protein levels in nontransfected cells. In various Chinese hamster ovary cell lines, the amounts of APP coprecipitated by PS **antibodies** were proportional to the expression levels of both APP and PS. APP-PS complexes also were recovered from human 293 and HS683 cells. Full maturation of APP was not required for the interaction; most APP molecules complexed with PS were solely N-glycosylated. Treatment of cells with brefeldin A or incubation at 20 degrees C did not block complex formation, suggesting that the association between APP and PS occurs in part in the endoplasmic reticulum. Complex formation was detected for both wt and mutant PS and APP proteins. Deletion of the APP C-terminal domain did not abrogate complex formation, suggesting that the interaction does not occur in the cytoplasmic domains of the proteins. Our results demonstrate that wt and mutant PS1 and PS2 proteins form complexes with APP in living cells, strongly supporting the hypothesis that mutant PS

interacts with APP in a way that enhances the intramembranous proteolysis of the latter by a gamma-secretase cleaving at Abeta42.

L2 ANSWER 7 OF 12 MEDLINE
AN 97329164 MEDLINE
DN 97329164 PubMed ID: 9185677
TI Chloroquine administration in mice increases **beta-amyloid** immunoreactivity and attenuates kainate-induced blood-brain barrier dysfunction.
AU Mielke J G; Murphy M P; Maritz J; Bengualid K M; Ivy G O
CS Department of Psychology, University of Toronto, Scarborough, ONT, Canada.
SO NEUROSCIENCE LETTERS, **(1997 May 23)** 227 (3) 169-72.
Journal code: N7N; 7600130. ISSN: 0304-3940.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970728
AB The anti-malarial drug chloroquine (CHL) has been reported to cause the accumulation of **beta-amyloid** peptide containing fragments (fA beta) of the amyloid precursor protein within lysosomes in vitro. However, the significance of this finding with regards to the development of Alzheimer's disease (AD) pathology in vivo is not known. Hence, we investigated the effects of chronic CHL administration in the mouse. Systemically administered CHL caused an astrocytic response and an increase in intracellular A beta immunoreactivity throughout the brain, but no plaque-like pathology. Pharmacological challenge with the excitotoxin kainic acid (KA) revealed a mild proconvulsant effect of CHL pretreatment ($P < 0.06$). Interestingly, CHL protected the blood-brain barrier from characteristic KA-induced dysfunction. Given the hypothesized involvement of both excitotoxic processes and the vascular system in AD, the observed interactions may assist in elucidating the pathogenesis of AD.

L2 ANSWER 8 OF 12 MEDLINE
AN 96303381 MEDLINE
DN 96303381 PubMed ID: 8744402
TI Accumulation of **beta-amyloid** fibrils in pancreas of **transgenic** mice.
CM Erratum in: Neurobiol Aging 1996 Jul-Aug;17(4):667
AU Kawarabayashi T; Shoji M; Sato M; Sasaki A; Ho L; Eckman C B; Prada C M; Younkin S G; Kobayashi T; Tada N; Matsubara E; Iizuka T; Harigaya Y; Kasai K; Hirai S
CS Department of Neurology, Gunma University School of Medicine, Japan.
SO NEUROBIOLOGY OF AGING, **(1996 Mar-Apr)** 17 (2) 215-22.
Journal code: NX5; 8100437. ISSN: 0197-4580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961106
Last Updated on STN: 19980206
Entered Medline: 19961024

AB Some forms of familial Alzheimer's disease are caused by mutations in the amyloid beta protein precursor (beta APP), and there is excellent evidence that these mutations foster amyloid deposition by increasing secretion of total amyloid beta protein (A beta) or the highly amyloidogenic A beta 1-42 form. These observations provide a powerful rationale for developing an animal model of AD by generating **transgenic** mice in which cerebral amyloid deposition is induced by A beta overproduction. To produce substantial A beta in vivo, we generated mice expressing the transgene of signal peptide and 99 residues of carboxyl-terminal fragment (CTF) of beta APP under control of the cytomegalovirus enhancer/chicken beta-actin promoter. The **transgenic** mRNA was detected in many tissues of these mice, but the levels of **transgenic** mRNA, CTF, and A beta did not correlate well indicating that tissue-specific posttranslational processing may play an important role in determining the amount of A beta that accumulates in various tissues. A beta was detected biochemically in brain, kidney, and pancreas with the largest amount present in pancreas. In **transgenic** plasma, there was a marked accumulation of human A beta 1-40 and A beta 1-42(43) to levels over 30-times those observed in normal human plasma. Thus, the **transgenic** mice produce and secrete considerable A beta. Despite this increase in A beta secretion and the elevated A beta in brain, immunohistochemistry revealed no consistent cerebral A beta deposition. In pancreas, however, intracellular A beta deposits were detected immunohistochemically in acinar cells and interstitial macrophages, some of which showed severe degeneration. In addition, examination of these cells by immunoelectron microscopy revealed many putative amyloid fibrils (7-12 nm) that were stained by anti-A beta **antibodies**. Overall, our findings indicate that tissue-specific posttranslational processing may play a pivotal role in A beta production and amyloid fibril formation in vivo. By carefully analyzing the changes that occur in the **transgenic** mice described here as compared to the **transgenic** line that has recently been shown to form extracellular amyloid plaques in brain, it may be possible to gain considerable insight into the factors that determine the location and amount of A beta that accumulates as amyloid.

L2 ANSWER 9 OF 12 MEDLINE
AN 96016170 MEDLINE
DN 96016170 PubMed ID: 7568134
TI Expression of human **beta-amyloid** peptide in **transgenic** Caenorhabditis elegans.
AU Link C D
CS Department of Biological Sciences, University of Denver, CO 80208, USA.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1995 Sep 26)** 92 (20) 9368-72.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951027
AB **Transgenic** Caenorhabditis elegans nematodes have been engineered to express potentially amyloidic human proteins. These animals contain constructs in which the muscle-specific unc-54 promoter/enhancer of C.

elegans drives the expression of the appropriate coding regions derived from human cDNA clones. Animals containing constructs expressing the 42-amino acid **beta-amyloid** peptide (derived from human amyloid precursor protein cDNA) produce muscle-specific deposits immunoreactive with anti-**beta-amyloid** polyclonal and monoclonal **antibodies**. A subset of these deposits also bind the amyloid-specific dye thioflavin S, indicating that these deposits have the tinctural characteristics of classic amyloid. Co-expression of beta-peptide and transthyretin, a protein implicated in preventing the formation of insoluble **beta-amyloid**, leads to a dramatic reduction in the number of dye-reactive deposits. These results suggest that this invertebrate model may be useful for in vivo investigation of factors that modulate amyloid formation.

L2 ANSWER 10 OF 12 MEDLINE
AN 94234692 MEDLINE
DN 94234692 PubMed ID: 7513982
TI **Transgenic** mouse brain histopathology resembles early Alzheimer's disease.
AU Higgins L S; Holtzman D M; Rabin J; Mobley W C; Cordell B
CS Scios Nova, Mountain View, CA 94043.
NC AG 10665 (NIA)
AG-00445 (NIA)
AG08938 (NIA)
SO ANNALS OF NEUROLOGY, **(1994 May)** 35 (5) 598-607.
Journal code: 6AE; 7707449. ISSN: 0364-5134.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199406
ED Entered STN: 19940620
Last Updated on STN: 19980206
Entered Medline: 19940609
AB **Transgenic** mice expressing the 751-amino acid form of the human amyloid precursor protein develop extracellular **beta-amyloid** protein (A beta)-immunoreactive deposits that increase in frequency with age. Here we show that the appearance and histological profile of deposits in the **transgenic** mice closely resemble those of preamyloid deposits in the brains of young adults with Down's syndrome, who presumably have the pathology of early-stage Alzheimer's disease. Specific monoclonal **antibodies** reveal that material in the deposits has the free carboxyl terminus of A beta 1-42, and that the deposits contain material which, by immunohistochemical analysis, apparently originates from the human **beta-amyloid** precursor protein (beta PP) transgene. In rare cases, the **transgenic** mouse brains contain several different histopathological characteristics of Alzheimer lesions. These features include dense A beta immunoreactivity which co-localizes with gliosis and with Alz50-immunoreactive structures resembling swollen boutons of dystrophic neurites. These observations demonstrate that the murine brain is capable of reproducing several typical features of Alzheimer histopathology.

L2 ANSWER 11 OF 12 MEDLINE
AN 94057832 MEDLINE
DN 94057832 PubMed ID: 8239286
TI **Transgenic** mice expressing human beta-APP751, but not mice expressing beta-APP695, display early Alzheimer's disease-like

histopathology.
AU Higgins L S; Catalano R; Quon D; Cordell B
CS Scios Nova Inc., Mountain View, California 94043.
NC RO1 AG10655-01 (NIA)
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(1993 Sep 24)** 695 224-7.
Journal code: 5NM; 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199312
ED Entered STN: 19940117
Last Updated on STN: 19980206
Entered Medline: 19931210
AB Mice **transgenic** for the 751 amino acid isoform of the human **beta-amyloid** precursor protein (beta-APP) driven by the rat neuron specific enolase (NSE) promoter (NSE:beta-APP751) show features of early Alzheimer's disease (AD) pathology. These features, which were evident in multiple pedigrees, include: 1) preamyloid deposits which stain with **antibodies** that are specific for the **beta-amyloid** peptide and stain AD amyloid deposits and plaques, and 2) neuronal soma and processes which stain with an **antibody** (Alz50) that detects abnormal isoforms of tau which are characteristic of AD. The quality and distribution of both types of immunoreactivity revealed in the NSE:beta-APP751 mouse brains most closely resemble those seen in brains of young adults with Down's syndrome. Both structures are rarely, if ever, observed in brains from mice **transgenic** for the 695 amino acid isoform of beta-APP (NSE:beta-APP695) or in wild type mice.

L2 ANSWER 12 OF 12 MEDLINE
AN 93066342 MEDLINE
DN 93066342 PubMed ID: 1438289
TI Deposition of beta/A4 immunoreactivity and neuronal pathology in **transgenic** mice expressing the carboxyl-terminal fragment of the Alzheimer amyloid precursor in the brain.
AU Kammesheidt A; Boyce F M; Spanoyannis A F; Cummings B J; Ortegon M; Cotman C; Vaught J L; Neve R L
CS Department of Psychobiology, University of California, Irvine 92717.
NC HD18658 (NICHD)
NO1-HD-0-2911 (NICHD)
NS28406 (NINDS)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Nov 15)** 89 (22) 10857-61.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199212
ED Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921223
AB The deposition of amyloid in senile plaques and along the walls of the cerebral vasculature is a characteristic feature of Alzheimer disease. The

peptide comprising the carboxyl-terminal 100 amino acids of the **beta-amyloid** precursor protein (beta APP) has been shown to aggregate into amyloid-like fibrils in vitro and to be neurotoxic, suggesting that this fragment may play a role in the etiology of Alzheimer disease. To address this question, we expressed this carboxyl-terminal 100-amino acid peptide of beta APP in **transgenic** mice under the control of the brain dystrophin promoter. We used an **antibody** to the principal component of amyloid, beta/A4, to demonstrate cell-body and neuropil accumulation of beta/A4 immunoreactivity in the brains of 4- and 6-month-old **transgenic** mice. Only light cytoplasmic staining with this **antibody** was visible in control mice. In addition, immunocytochemical analysis of the brains with an **antibody** to the carboxyl terminus of beta APP revealed abnormal aggregation of this epitope of beta APP within vesicular structures in the cytoplasm and in abnormal-appearing neurites in the CA2/3 region of the hippocampus in **transgenic** mice, similar to its aggregation in the cells of Alzheimer disease brains. Thioflavin S histochemistry suggested accumulations of amyloid in the cerebrovasculature of **transgenic** mice with the highest expression of the beta APP-C100 transgene. These observations suggest that expression of abnormal carboxyl-terminal subfragments of beta APP in vivo may cause amyloidogenesis and specific neuropathology.

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